

A CONTAINER COMPRISING NICOTINE AND THE USE AND MANUFACTURE THEREOF

This application hereby claims priority from Swedish patent application 0300520-4, filed February 28, 2003 and U.S. provisional application 60/458,159, filed March 27, 2003.

5 **Technical Field**

This invention relates to a container comprising nicotine. The container is for use in an inhaling device. Such a device is for use in nicotine replacement therapy treatment (NRT) and tobacco dependence treatment.

Background of the Invention

10 *Tobacco dependence and reduction thereof*

In recent years, with the recognition of the harmful effects of tobacco smoking, there have been numerous campaigns and programs by governmental agencies and various health groups and other interested organizations to disseminate information about the adverse health effects resulting from tobacco smoking. Moreover, and as a result of this recognition of the
15 harmful effects, there have been many programs directed to attempts in reducing smoking incidence.

Nicotine ($C_{10}H_{14}N_2$) is an organic compound and is the principal alkaloid of tobacco and it is the chief addictive ingredient in the tobacco used in cigarettes, cigars, snuff and the like. Nicotine is also an addictive drug and smokers characteristically display a strong
20 tendency to relapse after having successfully stopped smoking for a time. Nicotine is among the world's most used drug, along with alcohol and caffeine from coffee and tea. It is an addictive poisonous alkaloid. And it is also used as an insecticide. The minimal acute lethal dose of nicotine in human adults is 40 to 60 mg.

The main problem with tobacco smoking is its enormous implications on health. Today
25 it is estimated that smoking-related diseases cause some 3-4 million deaths per year. It was estimated, in the US Surgeon General's 1988 report on The Health Consequences of Smoking, that in the US alone diseases related to cigarette smoking cause about 300.000 deaths each year. In fact, excessive smoking is now recognized as one of the major health problems throughout the world. This grim consequence of tobacco smoking has urged many
30 medical associations and health authorities to take very strong actions against the use of tobacco.

Even though tobacco smoking is decreasing in many developed countries today it is hard to see how the societies could get rid of the world's second most used drug or even

decrease the use thereof.

The most advantageous thing a heavy smoker can do is to completely stop, or at least reduce, his/her smoking. Experience shows, however, that most smokers find it extremely difficult to stop or even to reduce smoking since, mostly, smoking tobacco result in a dependence disorder or craving. The WHO has in its International Classification of Disorders a diagnosis called Tobacco Dependence. Others like the American Psychiatric Association call the addiction Nicotine Dependence. It is generally accepted that these difficulties to stop or reduce smoking result from the fact that those heavy smokers are dependent on nicotine. The most important risk factors are, however, substances that are formed during the combustion of tobacco, such as carbon monoxide, tar products, aldehydes, and hydrocyanic acid.

Effects of nicotine

The administration of nicotine usually provides a pleasant feeling. The usual method of administration is by intake via the mouth, either by smoking e.g. a cigarette, a cigar or a pipe, or snuffing or chewing tobacco. However, smoking has, as earlier mentioned, health hazards and it is therefore desirable to formulate an alternative manner of administering nicotine in a pleasurable manner that can be used to facilitate withdrawal from smoking and/or used as a replacement for smoking.

Upon the smoking of a cigarette, nicotine is quickly absorbed into the smoker's blood and reaches the brain within around ten seconds after inhalation. This quick uptake of nicotine gives the consumer a rapid satisfaction, or kick, and this satisfaction lasts during the smoking time of the cigarette and for a period of time thereafter. The poisonous, toxic, carcinogenic, and addictive nature of smoking has provided efforts for methods, compositions and devices, which help in breaking the habit of smoking cigarettes.

Nicotine replacement products

One way to reduce smoking is to provide nicotine in a form or manner other than by smoking and some products have been developed to fulfill this need. Use of such nicotine-containing formulations is currently the dominating treatment for tobacco dependence.

The present successes in achieving reduction in the incidence of smoking have been relatively poor using presently known products. The present state of the art involves both behavioral approaches and pharmacological approaches. More than 80 % of the tobacco smokers who initially quit smoking after using some behavioral or pharmacological approach to singly reduce smoking incidence generally relapse and return to the habit of smoking at their former rate of smoking within about a one year's period of time.

As an aid for those who are willing to stop smoking there are several ways and forms of nicotine replacement products available on the market and several methods and means have been described for diminishing the desire of a subject to use tobacco, which comprises the step of administering to the subject nicotine or a derivative thereof as described in e.g. US 4,967,773 (nicotine containing lozenge) and US 5,939,100 (nicotine containing microspheres).

The use of skin patches for transdermal administration of nicotine has been reported (Rose, in Pharmacologic Treatment of Tobacco Dependence, (1986) pp. 158-166, Harvard Univ. Press). Nicotine-containing skin patches, which are in wide use today, may cause local irritation and the absorption of nicotine is slow and affected by cutaneous blood flow. Different types of such patches are also patented, see e.g. US 4,915,950 and US 4,597,961.

Nicotine-containing nose drops have been reported (Russell et al., British Medical Journal, Vol. 286, p. 683 (1983); Jarvis et al., British Journal of Addiction, Vol. 82, p. 983 (1987)). Nose drops, however, are difficult to administer and are not convenient to use at work or in other public situations. Ways of administering nicotine by delivering directly into the nasal cavity by spraying are known from US 4,579,858, DE 32 41 437 and WO 93/12764. There may, though, be local nasal irritation with use of nasal nicotine formulations. The difficulty in administration also results in unpredictability of the dose of nicotine administered.

Nicotine mouth sprays (see e.g. US 6,024,097 and US 5,810,018) and nicotine chewing gums (see e.g. US 3,845,217) are also known.

Also, inhaling devices resembling a cigarette are known for uptake of nicotine vapors orally as suggested in US 5,167,242, wherein the inhaling device contains a nicotine reservoir. The present invention relates primarily, but not exclusively, to a novel and inventive improvement of the nicotine reservoir (plug) disclosed in US 5,167,242.

Prior art and problems thereof

One embodiment of the inhaling device disclosed in US 5,167,242 comprises a cylindrical cartridge in which is placed a nicotine reservoir. Such a reservoir consists of a porous plug made of polymer or other suitable material, which is loaded with nicotine. Suitable materials for such a plug are e.g. those mentioned in US 4,284,089, US 4,800,903 and US 4,813,437 e.g. polymeric material containing polyolefin, polyethylene, polypropylene, polybutadiene, poly-1-butene, polyisobutylene, polyisoprene, poly-4-methyl-1-pentene or combinations thereof, a fibrous material which may comprise cellulose-acetate polypropylene, polyester, polyethylene and combinations thereof. The above-mentioned

porous plugs are manufactured through a sintering process. US 4,793,366 discloses a device for inhaling nicotine with a “draw” similar to that of a conventional cigarette – though without showing that such a “draw” may be obtained with the claimed device. US 5,101,838 discloses a device for smoking simulation where the carrier for nicotine preferably is made of spherical particles. US 5,167,242, US 4,284,089, US 4,800,903, US 4,813,437, US 4,793,366 and US 5,101,838 are hereby incorporated by reference.

The presently known porous nicotine containing plug releases nicotine to the air sucked through it by the user when the user puff on the inhaling device. However, it has now been found that the user does not inhale enough nicotine per puff (Schneider et al.; Clin. Pharmacokinetics 2001; 40 (9) 661-684 and Russel; British J. of Addiction (1991) 86, 653-658) in order to experience complete satisfaction. Therefore the user must puff intensively in order to achieve a basal, but oftentimes still non-sufficient, concentration of drug (Schneider et al.; Clin. Pharmacokinetics 2001; 40 (9) 661-684). Hence, such an inhaling device often does not sufficiently well counteract the craving experience by the tobacco addict, who therefore is likely to relapse to use of tobacco. To date no solution to the problem of the user not inhaling enough nicotine per puff has been presented.

Definitions

The term “nicotine” is intended to include nicotine, 3-(1-methyl-2-pyrrolidinyl)-pyridine, with its base form, racemic form, R- and S-forms, including synthetic nicotine as well as nicotine extracts from tobacco plants, or parts thereof, such as the genus *Nicotiana* alone or in combination; or pharmaceutically acceptable salts.

The term “container comprising nicotine”, or equivalent terms, is intended to include a nicotine reservoir loaded with nicotine that will allow air to pass through and that will deliver nicotine in gaseous or liquid aerosol form to a subject.

The term “fast reduction of the urge to smoke or use tobacco” is herein intended to mean an initial priming of the subject so as to achieve a reduction of the urge to smoke or use tobacco.

The term “complete reduction” is herein intended to mean complete or substantially complete reduction.

The terms “fibers” and “filaments” are intended to mean any of the thread-like parts that are formed from plant and/or artificial material with arbitrary cross sections.

The term “tobacco-containing material” may be material used for e.g. smoking, snuffing or chewing and may comprise a cigarette, a cigar, snuff, pipe tobacco and chewing tobacco.

The term “shaped mass” is intended to mean a mass of material deliberately shaped.

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Summary of the Invention

The present invention is intended to solve the above-mentioned problem, i.e. that the user does not receive enough nicotine per puff to experience satisfaction. We have however found that said problem couldn't be solved by increasing the amount of nicotine in the container since the air inhaled with the existing device is already saturated with nicotine and hence cannot be loaded with more nicotine. In the present invention we have surprisingly found said problem is solved by increasing the volume of air inhaled per puff thereby increasing the amount of nicotine being inhaled per puff - this being achieved by using a nicotine container comprising a shaped mass of fibers or filaments.

The main object of the present invention is thus to provide a container comprising nicotine and a shaped mass of fibers or filaments, which is able to reversibly retain and release nicotine. This container allow a larger amount of air being inhaled per puff and also provide that the air is inhaled with less efforts compared to the above-mentioned presently known plugs. The flow resistance through the present container is thus lower than the flow resistance through the existing plugs. It has also been found that with the present invention the flow resistance may be lowered to below a half, and even below a fourth, of the flow resistance of presently used plugs in nicotine inhalers. The air passing through the container is adequately saturated with nicotine in spite of the low airflow resistance.

The present invention also provides a method for obtaining reduction of the urge to smoke or use tobacco containing material and/or for providing a fast sense of smoking satisfaction without smoking, comprising the steps of replacing at least partly the tobacco containing material used with an inhaling device that comprises the above-mentioned container comprising nicotine.

Furthermore, the present invention also provides a system for delivering nicotine to a subject, which comprises said container comprising nicotine and at least one other means for obtaining reduction of the urge to smoke or use of tobacco and a system for obtaining reduction of the urge to smoke or otherwise use of tobacco and/or for providing a sense of smoking satisfaction without smoking, comprising said container comprising nicotine and at least one other method for obtaining reduction of the urge to smoke or otherwise use of tobacco. Said system may be a system wherein the at least one other method is selected from the group consisting of administration through chewing gums, nasal sprays, transdermal patches, mouth sprays, lozenges, tablets and parenteral methods, subcutaneous methods, intravenous methods, rectal methods, vaginal methods and transmucousal methods; or otherwise use of tobacco.

The present invention also relates to the use of said product that will according to the invention rapidly deliver nicotine to a subject and also to the use of the present invention for obtaining a quick and/or sustained and/or complete reduction of the urge to smoke or use tobacco and/or for providing a sense of smoking satisfaction without smoking resembling the sense of smoking satisfaction and/or for obtaining a reduction of the urge to smoke obtained after regular smoking or use of tobacco.

Detailed Description of the Invention

In one embodiment said container comprising nicotine has fibers or filaments that comprise polymeric substances. The polymeric substances may be selected from polyolefin, polyester or polyamide and are preferably selected from the group consisting of polyethylene, polyethylene, preferably high-density polyethylene or ultra high molecular weight polyethylene, polypropylene, polybutadiene, poly-1-butene, polyisobutene, polyisoprene, polyvinylidene chloride, ethylene vinyl alcohol, polylactide-glycolide copolymer, polycarbonate, polyethylene naphthalene, polytrimethylene naphthalene, polyethylene terephthalate, terephthalate-isophthalate polyesters, polybutylene terephthalate, liquid crystalline polymer that comprises hydroxy benzoic acid and hydroxy naphthenic acid, a copolymer of acrylonitrile and methacrylate grafted to nitrile rubber, which is commercially available under the trademark Barex[®], nylon 66, or nylon 6 or combinations thereof and paper, cellulose and/or cloth. Preferably the fibers or filaments are non-sintered. The container may though comprise also non-sintered material. The fibers or filaments may comprise also non-polymeric materials, such as glass, metals, e g aluminum and/or steel. The fibers or filaments may optionally be coated.

The container may also comprise non-fibrous material. Preferably the shaped mass of fibers or filaments is non-sintered. The container may though comprise also non-sintered material. The shaped mass of fibers or filaments may comprise non-polymeric material, such as glass, metals, e g aluminum and/or steel, paper, cellulose and/or cloth.

A preferred type of fibers or filaments is made of polyethylene terephthalate, preferably covered with copolyolefin.

The fibers or filaments may be manufactured in a number of different ways known in the art, such as through extrusion and spinning.

Preferably the container should have a flow resistance of gas being lower than around 0,6 kPa, more preferably lower than around 0,3 kPa at an airflow rate of 1000 ml/min.

The nicotine is preferably retained to the shaped mass of fibers or filaments by

chemical binding and/or by adsorption and/or by absorption and released by breaking these mechanisms. The absorption and/or adsorption processes, which release nicotine may further be electrically enhanced and/or modified by temperature.

5 The container is for use in a nicotine-inhaling device, which is adapted to be received in the mouth or in the nose.

The container should preferably be encapsulated in such a way that nicotine will not unintentionally migrate out from the container and so that environmental oxygen will not enter the container. For such encapsulation of the container a nicotine-impermeable copolymer made of acrylonitrile and methacrylate and grafted to nitrile rubber can be used, said copolymer being commercially available under the trademark Barex[®]. Polyethylene
10 naphthalate, known under the name PEN, and/or a liquid crystalline polymer comprising hydroxy benzoic acid and hydroxy naphthenic acid, known under the name Vectra[®] A530, can also be used for such encapsulation. Optionally said polymers can be laminated, e g with aluminum layer. Preferably said encapsulation should be made in an oxygen-free
15 environment. Upon use of the container the encapsulation is broken in order for the user to inhale through the container. Said encapsulation is essence is done according to the disclosure of the above-mentioned patent US 5,167,242.

Methods of production

20 One preferred embodiment of loading the containers with nicotine is to let a gas comprising nicotine pass through the containers thus allowing the nicotine to be absorbed and/or adsorbed by the material of the container.

Another preferred embodiment of loading the containers with nicotine is immersing the containers into a solution comprising nicotine in its free base form. Preferably the solvent
25 is an organic solvent, preferably an organic solvent having a low boiling point and being more volatile than nicotine, more preferably an organic solvent being selected from the group of ethers, ketons and alcohols, even more preferably being an organic solvent being selected from alcohols, and most preferably being ethanol.

Still another preferred embodiment of loading the containers with nicotine is to inject
30 a solution comprising nicotine, with e.g. a syringe, in the containers.

The containers may also be loaded with nicotine by spraying or soaking or immersing the fibers or filaments with nicotine or with a nicotine-containing liquid directly upon the fibers or filaments, and the optional non-fibrous material, having been manufactured, e g

upon them having been extruded or spun, prior to the fibers or filaments being formed to a shaped mass. The same loading principle could be applied if the containers optionally comprise also non-fibrous material.

Different additives may optionally be added to the containers, e g one or more stabilizing additives, such as those selected from the group consisting of antioxidants including vitamin E, i.e. tocopheroles, vitamin C, i.e. ascorbic acid, sodium pyrosulfite, butylhydroxytoluene, butylated hydroxyanisole; and preservatives including parabenes, citric acid, tartaric acid, lactic acid, malic acid, acetic acid, benzoic acid, and sorbic acid; and chelating agents, such as EDTA; and galates, such as propyl galate.

Further optional additives can comprise one or more additives selected from the group consisting of enhancers, such as azone, vitamins, such as vitamins B, C and E, minerals, such as fluorides, especially sodium fluoride, sodium monofluoro phosphate and stannous fluoride, anti-odors, such as zinc and cyclodextrins, propellants, such as 1,1,2,2-tetrafluoroethane (HFC-134a), optionally being liquefied, and 1,1,1,2,3,3, 3-heptafluoropropane (HFC-227), optionally being liquefied, sweeteners including one or more synthetic or natural sugars, such as those selected from the group consisting of artificial sweeteners such as saccharin, sodium saccharin, aspartame, e g NutraSweet, acesulfame or acesulfame K (also called potassium acesulfame), thaumatin and glycyrrhizin; sugar alcohols, such as sorbitol, xylitol, single sugars including sugars extracted from sugar cane and sugar beet (sucrose), dextrose (also called glucose), fructose (also called laevulose), and lactose (also called milk sugar); mannitol, glycerol; and mixtures of sugars including glucose syrup, e g starch hydrolysates, containing a mixture of dextrose, maltose and a range of complex sugars, invert sugar syrup, e g sucrose inverted by invertase (also called sucrase or sacchrase) containing a mixture of dextrose and fructose, high sugar content syrups such as treacle and honey containing a mixture of particularly laevulose, dextrose, maltose, lactitole, sucrose, resins, dextrin and higher sugars; and malt or malt extracts; and mixtures thereof.

Flavor and aroma additives can also be added. These may comprise one or more synthetic or natural flavoring or aromatizing agents. Flavor and aroma agents may be selected from the group comprising essential oils and preparations thereof including distillations, solvent extractions, or cold expressions of chopped flowers, leaves, peel or pulped whole fruit comprising mixtures of alcohol, esters, aldehydes and lactones; essences including either diluted solutions of essential oils, or mixtures of synthetic chemicals blended to match the natural flavor of the fruit, e g strawberry, raspberry and black currant; artificial and natural flavors of brews and liquors, e.g. cognac, whisky, rum, gin, sherry, port, and wine; tobacco,

coffee, tea, cocoa, and mint; fruit juices including expelled juice from washed, scrubbed fruits such as lemon, orange, and lime; spear mint, pepper mint, wintergreen, cacao/cocoa, vanilla, liquorice, menthol, eucalyptus, aniseeds, nuts, e.g. peanuts, coconuts, hazelnuts, chestnuts, walnuts, cola nuts; almonds, raisins; barks, e.g. cinnamon, roots, e.g. ginger, and mixtures thereof.

The nicotine should be in gaseous or liquid aerosol form when inhaled in order to facilitate the absorption and uptake anywhere in the mouth or oral cavity and/or the upper respiratory tract and/or lungs.

The nicotine may act as a substituted stimulant e.g. to obtain a rapid reduction of the urge to smoke or to use tobacco. The effect may be to provide a sense of smoking satisfaction without smoking. Another effect of the administered nicotine may be a reduction of the urge to smoke or use tobacco.

The effect may also be a combination of reduction of said urge and providing a sense of smoking satisfaction without smoking. The amount of the nicotine should be sufficient to provide such an effect in a subject. This amount may, of course, vary from person to person.

Example 1

Process for the manufacturing of nicotine-comprising containers with 15 mg nicotine/container for use with inhaling devices

Manufacturing formula:

Batch size: 100 000 units

Formula:

Loading solution:

Nicotine	1 545 g
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Levomenthol	150 g
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Ethanol*	16 000 g
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*Removed during manufacture

Loading of containers:

Containers from a shaped mass of fibers or filaments of polyethylene

terephthalate covered with a

copolyolefin sheath.	100 000 pieces
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Loading solution	17 695 g
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Nitrogen	q.s.
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Assembly:

Nicotine-loaded containers 100 000 pieces

Plastic cartridges made of Barex[®] 100 000 pieces

Barex[®]-coated aluminum foil q.s.

5 Nitrogen q.s.

The manufacturing phases were:

Loading solution:

Levomenthol and nicotine were dissolved in ethanol.

Loading of containers:

10 The containers were added to a vacuum cone blender. The loading solution was added to a blender and the containers were mixed with the loading solution. A vacuum was applied and the temperature was increased to about 50°C in order to remove ethanol. The drying process was terminated by cooling the jacket of the blender. The nicotine-loaded containers were transferred to airtight bulk containers, which were evacuated and filled with nitrogen.

15 Assembly and sealing:

The assembly of the nicotine-loaded containers into the plastic cartridges was performed in separated zones, involving feeding of the containers and cartridges from a first zone, and the subsequent assembly in a second zone. Sealing of the plastic cartridges was made by welding with Barex[®]-coated aluminum foil. All zones were separately fed with nitrogen.

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Method for delivering nicotine to a subject

According to the invention, a method for delivering nicotine to a subject comprises the steps of

a) administering to a subject air loaded with nicotine by using an inhalation device
25 containing the container comprising nicotine and

b) allowing the nicotine to be released in the mouth/oral cavity and/or the upper respiratory tract and/or the lungs and then being absorbed into the blood plasma of the subject.

Method for obtaining reduction of the urge to smoke or use of tobacco

30 A method for obtaining reduction of the urge to smoke or use tobacco-containing material and/or for providing a sense of smoking satisfaction without smoking according to the invention comprises the steps of:

a) replacing at least partly the tobacco containing material with an inhaling device

comprising the container comprising nicotine,

b) administering to a subject nicotine according with the help of the container comprising nicotine into the oral cavity and/or the upper respiratory tract and/or the lungs of the subject, and

5 c) allowing the nicotine to be absorbed by the subject.

The administration of nicotine takes place by the subject inhaling air loaded with nicotine i.e. the subject puffs on the inhaler comprising the container comprising nicotine as the air passes said container the nicotine is released from said container and the subject will thus receive air loaded with nicotine. The administration is essentially intended for the
10 mouth/oral cavity and/or the upper respiratory tract and/or the lungs.

Even further embodiments of the method for delivering nicotine to a subject may comprise the steps of combining the method of using the present inhaling device with at least one other method for obtaining reduction of the urge to smoke or use of tobacco.

The container comprising nicotine may be used for obtaining a quick and/or sustained
15 and/or complete reduction of the urge to smoke or use of tobacco and/or for providing a sense of smoking satisfaction without smoking as further discussed below. The fast relief provides the subject with a sense of rapid smoking satisfaction without smoking.

Systems for delivering nicotine and for obtaining craving relief

According to the present invention is also provided a system for delivering nicotine to a
20 subject. Such a system comprises the container comprising nicotine according to the present invention and an inhalation device, and at least one other means for obtaining reduction of the urge to smoke.

Another system according to the invention may also be a system for obtaining reduction of the urge to smoke or use of tobacco and/or for providing a sense of smoking satisfaction
25 without smoking. Such a system comprises the container comprising nicotine according to the invention and at least one other means for obtaining reduction of the urge to smoke or use tobacco. Other means/methods may also be a concomitant or concurrent method selected from the group consisting of administration through nasal sprays, transdermal patches, lozenges, tablets and parenteral methods, subcutaneous methods, intravenous methods, rectal
30 methods, vaginal methods and transmucosal methods; or use of tobacco.

In a specific embodiment, the at least one other method/method comprises administration of nicotine.

Use of the container comprising nicotine

The use of the container comprising nicotine according to the invention for obtaining a fast and/or sustained and/or complete reduction of the urge to smoke and use tobacco or for providing a sense of smoking without smoking as described above.

- 5 The dose of the nicotine is chosen to give the subject an individual sensory perception and nicotine satisfaction. The use of the container comprising nicotine according to the invention may also be a sole use according to the invention or a combination with other means or methods known in the field of drug abuse. Specifically, the present invention may be used in combination with other means as described above in the methods in the paragraphs
- 10 above. The use may give a quick reduction of the urge to smoke or use tobacco.